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14. ABSTRACT The purpose of this research effort is to conduct a randomized controlled trial (RCT): "Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness" which will evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI. The primary activities conducted during year three of the project involved continued coordination with the Madison Veterans Affairs Hospital (VA) for subject identification and recruitment, and subject recruitment and enrollment.					
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INTRODUCTION

More than 50,000 troops returned from the Persian Gulf conflicts reporting a myriad of medically unexplained symptoms with no identifiable etiology. While patients who meet the case definition of Gulf War Illness (GWI) can have a myriad of symptoms, two of the most prevalent and debilitating ones are chronic nasal congestion and fatigue. The purpose of this research effort is to conduct a randomized controlled trial (RCT): “Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness” which will evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI.

BODY

The major objectives of the study are twofold: 1) To find an effective adjunctive therapy for veterans with Gulf War Illness (GWI) and symptoms of chronic rhinosinusitis (CRS) and fatigue and 2) To evaluate the proinflammatory bias of each individual’s profile at baseline and in response to therapy. Statistically positive results on clinical outcome measures would demonstrate that nasal irrigation (NI) can provide effective adjunctive therapy for CRS and fatigue, improving quality of life for GWI-affected patients and potentially to society through reduced use of medical resources and absenteeism. Positive findings on cytokine and cellular assessment would shed light on the etiology of CRS and fatigue in the GWI population and contribute to the understanding of each; positive response to therapy would elucidate a biological mechanism of action of NI. Finally, the finding that NI, adjunctive to routine care, is more cost effective than “routine care only” would provide economic justification for its clinical use in the studied population.

The primary activities conducted during year four of the project involved the enrollment, retention, coordination and management of study subjects and data collection. Currently, the study has enrolled 44 subjects, 16 of whom have completed the study. There are 10 subjects who have passed the telephone screen and are potentially eligible; 5 of these potential participants have been scheduled for secondary screen and if eligible, will be scheduled for enrollment in the upcoming weeks. The remaining 5 eligible participants will soon be scheduled as we resolve participant scheduling conflicts.

Data entry and management via the secure study database is ongoing. The updated subject database has been invaluable in tracking enrolled subjects.

The study mechanics are functioning well; randomization is producing 3 comparable groups; all data acquisition is going well with high data capture rates.

The study design for initial subject identification primarily uses an ICD-9 code screen to identify veterans who were in the first Gulf War and with the appropriate diagnoses for chronic rhinosinusitis or fatigue in the past two years [CRS (473.*) or fatigue (780.7)]. As potential subjects are identified, we conduct outreach through mailings and have obtained approval from the UW Health Sciences IRB for an expanded protocol. The protocol included community recruitment methods such as tear-off flyers in public places veterans might frequent, presentations of study information to VFW and other veterans groups and electronic informational advertisements posted on VFW websites and listservs. These recruitment

methods are designed to identify veterans who receive care outside the VA system. We also expanded this pool of additional potential subjects by screening the billing ICD-9 databases of other VA hospitals in the VISN-12 network (VA Great Lakes Health Care System). This has provided us with access to Gulf War Veterans living in Milwaukee, WI; Chicago, IL, and surrounding areas. An earlier request made to the office of the Chief of Staff of the Madison VA Hospital for expansion of recruitment to the VISN-12 network was approved.

The study has obtained and maintained over the life of the award appropriate approvals from all relevant regulatory bodies including the UW Institutional Review Board, the VA Research Committee and the USAMRMC/Human Research Protections Office.

The manufacturer (Danisco/Dupont) of xylitol has continued to provide daily use packets at no cost as indicated in the protocol and letter of support in the initial grant application.

The table below is a summary of eligible and/or enrolled subjects recruited from the VA and the community during the reporting period.

	VA Recruitment	Community Recruitment	Total
Eligible subjects	50	5	55
Enrolled subjects	41	3	44

As study activities progress, study team members will continue to meet with staff associated with the UW Clinical Research Unit (CRU) to review clinical services to be utilized by the study as well as the Pharmaceutical Research Center (PRC) which will be housing and dispensing all study medications (Xylitol and Saline). We have final approval on all procedures associated with these two entities and continue to enroll and schedule subjects.

The study has undergone a random/routine institutional audit by the University of Wisconsin Institute of Clinical and Translational Research. The audit was completed with very positive feedback and minor suggestions were made for maximizing study quality.

The project recently received an approval for a 2nd-no cost extension of the grant award from July 1, 2015 to June 30, 2016. This application was necessary to further enrollment, complete participant follow-up of all enrolled participants, analyze data and prepare manuscripts. The extension period will be used exclusively to continue recruitment/study conduct/follow-up of participants as described in the original approved study protocol; no new methods, recruitment practices or analyses will be undertaken in the second EWOFF period. The project has received approval of this submission and will continue with planned study activities.

Interim analysis on data collected through 3-31-2015 has yielded data for submission to a national conference focused on bringing integrative medicine modalities such as nasal irrigation to underserved patient populations including veterans. The abstract has been accepted for presentation at <https://www.im4us.org/2015+Call+for+Speakers>. The baseline and 8-week follow-up data suggest that randomization has created three balanced groups which appear to be improving on the primary outcome measure (SNOT-20); and that interim results are especially promising for the saline group. The full abstract is provided below.

KEY RESEARCH ACCOMPLISHMENTS:

- Study approval from all relevant stakeholders (UW HS IRB, VA R & D Committee, DHSC)
- Expansion of recruitment strategies
- Procurement of xylitol
- Recruitment and enrollment of subjects

REPORTABLE OUTCOMES:

- UW HS IRB continuing review study approval
- Refinement of study tracking database

Upcoming activities planned for the project include:

- Continued recruitment and enrollment of study participants
- Continued participants follow up
- Data entry, cleaning and analysis
- Manuscript preparation

CONCLUSION: As stated, the purpose of this research effort is to evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI. While there have been inevitable practical and administrative hurdles, and the study team is new to research work within Veterans Administration structures, the study has continued enrollment and collection of high quality data. General success for either form of NI compared to routine care would provide an immediately accessible treatment to improve the quality of life of veterans with GWI, CRS and fatigue. Because of the likely overlap between the underlying etiologies of CRS and fatigue between GWI vets and the general population, success may also translate to a more general population. Positive findings would suggest a number of important effects:

- Statistically positive results on HRQoL outcome measures would suggest that NI can provide effective adjunctive therapy for CRS and fatigue in adults with GWI, improving health of affected patients and potentially providing gains to society through reduced health care utilization and absenteeism related costs.
- Positive biomarker findings would contribute to our better understanding of the etiology of CRS and fatigue in the GWI population and of possible biological pathways underlying the NI efficacy.
- The finding that either form of NI is cost effective would provide economic justification for its clinical use.

PUBLICATIONS, ABSTRACTS:

Publication

Supriya Hayer MD, David Rabago MD, Iliya Amaza MD MPH, Tony Kille MD, Aleksandra Zgierska MD PhD, Larissa Zakletskaia, MA, Dean Krahn MD, Chidi Obasi MD MS PhD, Rachel

Molander MD. *Effectiveness of Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness: Protocol for a Randomized Controlled Trial*. Contemp Clin Trials. 2015 Mar;41:219-26. doi: 10.1016/j.cct.2015.01.008. Epub 2015 Jan 24. PMID:25625809

Abstract

Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness: Preliminary data from a 3-arm randomized controlled trial. Chidi Obasi, MD PhD; Supriya Hayer MD; Tony Kille, MD; Rachel Molander, MD; Ian Hauffe; Ina Kansariwala; Daniel Fehrenbach; Lily Comp; David Rabago, MD. To be presented at the 2015 Integrative Medicine for the Underserved conference in Tuft University Boston, MA.

REFERENCES: NA

APPENDICES:

Attachment A: UW HS IRB Continuing Review approval – VA protocol
Attachment B: UW HS IRB Continuing Review approval – community protocol
Attachment C: Peer-reviewed publication
Attachment D: Abstract submitted and accepted



Health Sciences IRB

4/7/2015

**Submission ID
number:**

[2011-0843-CR003](#)

Title:

Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness(GW100054)

**Principal
Investigator:**

RACHEL C MOLANDER

Point-of-contact: CHIDI N OBASI

IRB Staff Reviewer: EMILY JENNER

The convened HS IRB conducted a full review of the above-referenced continuing review progress report. The study was approved for the period of 12 months with the expiration date of 4/5/2016.

IMPORTANT: This study falls under the criteria outlined in the Five Year Renewal Policy. As a result, no further continuing review applications can be submitted for this study unless this study qualifies for an exception as described in the HS-IRB's Exception to the Five Year Renewal Policy [<https://kb.wisc.edu/gsadminkb/page.php?id=29794>]. If this study does not qualify for an exception to the five year renewal policy, a replacement initial review application must be submitted. The replacement application must be submitted **no later than November 7, 2015**.

To access the materials approved by the IRB, including any stamped consent forms and recruitment materials, please log in to your ARROW account and view the documents tab in the submission's workspace.

Please review the Investigator Responsibilities guidance (<http://go.wisc.edu/m0lovn>) , which includes a description of IRB requirements for submitting continuing review progress reports, changes of protocol and reportable events.

Please contact the appropriate IRB office with general questions: Health Sciences IRBs at 608-263-2362 or Education and Social/Behavioral Science IRB at 608-263-2320. For questions related to this submission, contact the assigned staff reviewer.



Health Sciences IRB
3/25/2015

**Submission ID
number:**

[2012-1126-CR002](#)

Title:

Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in
Patients
with Gulf War Illness - Community Recruitment

**Principal
Investigator:**

DAVID P RABAGO

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CHIDI N OBASI

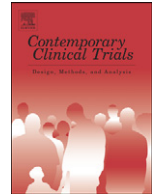
IRB Staff Reviewer: EMILY JENNER

The convened HS IRB conducted a full review of the above-referenced continuing review progress report. The study was approved for the period of 12 months with the expiration date of 3/23/2016.

To access the materials approved by the IRB, including any stamped consent forms and recruitment materials, please log in to your ARROW account and view the documents tab in the submission's workspace.

Please review the Investigator Responsibilities guidance (<http://go.wisc.edu/m0lovn>) , which includes a description of IRB requirements for submitting continuing review progress reports, changes of protocol and reportable events.

Please contact the appropriate IRB office with general questions: Health Sciences IRBs at 608-263-2362 or Education and Social/Behavioral Science IRB at 608-263-2320. For questions related to this submission, contact the assigned staff reviewer.



Effectiveness of nasal irrigation for chronic rhinosinusitis and fatigue in patients with Gulf War illness: Protocol for a randomized controlled trial ☆☆☆

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ABSTRACT

Introduction: Gulf War Illness (GWI) affects 1 in 7 returned Persian Gulf War veterans. Quality of life impact is large; there is no cure. Chronic sinus symptoms and fatigue are common. Nasal irrigation with saline (NI S) or xylitol (NI X) improve sinus symptoms and fatigue in the general population. This trial will assess the effect of NI S and NI X on sinus and fatigue symptoms, economic outcomes and pro-inflammatory milieu among participants with GWI.

Methods: 75 participants (age 35 to 65 years, 25 in each of three arms) with GWI will be recruited from the Veteran's Administration and the community. They will use routine care for sinus symptoms and fatigue and be randomized to continued usual care alone or additional therapy with NI S or NI X. Participants will be able to adjust specific elements of the NI procedure. The primary outcome (Sinonasal Outcome Test, SNOT 20) and other self-reported assessments will occur at baseline, 8 and 26 weeks; lab assessment of pro-inflammatory cellular and cytokine profiles will occur at baseline and 26 weeks. Other outcomes will include fatigue specific and overall health related quality of life, pro-inflammatory cellular and cytokine profiles, cost effectiveness and participant satisfaction.

Results: Baseline demographic and clinical data from the first 10 participants show effective participant recruitment, enrollment, randomization, retention and data collection.

Conclusion: Early study conduct suggests that our participant oriented approach will yield high rates of participant adherence and data capture, facilitating robust analysis. Results of this study will clarify the value of NI for chronic sinus symptoms and fatigue among patients with GWI.

Clinical trial registration: clinicaltrials.gov identifier NCT01700725.

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1. Introduction

Of the 700,000 veterans who returned from the Persian Gulf conflict of 1990–91 (Desert Shield/Desert Storm), up to 100,000 are affected by Gulf War Illness (GWI) [1,2]. Symptoms and co morbidities span multiple organ systems; the first and third most common complaints have been reported to be chronic upper respiratory complaints (with nasal congestion reported by 47% of patients) and fatigue (41%) [3,4].

The etiology of chronic upper respiratory complaints and fatigue among patients with GWI is unclear. In the general population, chronic upper respiratory symptoms are primarily caused by infectious, irritant and allergic agents. Chronic symptoms change the nasal mucosa, predisposing it to further insult. Fatigue is often concomitant with URI symptoms [5]. Change in the concentration of pro inflammatory biomarkers in serum and nasal mucosa has been associated with both fatigue [6] and chronic upper respiratory infection [7] in the general population. In spite of substantial research [8], and conflict about the status and relevance of that research [9], the cause and optimal treatment of GWI remain poorly understood. Therapy has focused on symptomatic treatment. The US Department of Defense (DoD) Gulf War Illness Research Program (GWRP) has called for investigation of therapy to treat GWI [8].

Nasal irrigation (NI) is an adjunctive treatment for chronic upper respiratory symptoms for a variety of conditions that bathes the nasal cavity with liquid [10,11]. Two solutions have been assessed, saline (NI S) and xylitol (NI X). NI S originated in the Ayurvedic medical tradition. Chronic rhinosinusitis (CRS) is the most common indication for NI S [10]. The Cochrane Collaboration concluded that NI S is appropriate adjunctive therapy for the symptoms of chronic rhinosinusitis [12]. An element of successful clinical use of NI S has been patient centered control of some elements of the irrigation protocol, including the frequency of irrigations and salinity, and has led to improved patient self management of symptoms and QoL, and decreased side effects [13]. NI X has a shorter clinical and cultural history, with medical use spanning only a few decades [14]. Xylitol is a naturally occurring, non absorbed, five carbon sugar reported to increase the effectiveness of resident natural killer cells in the nasal mucosa when used topically [15]. Xylitol has been reported to prevent dental caries [16] and acute otitis media [17]. It has been assessed for chronic upper respiratory symptoms in limited trials [12]. Neither NI S nor NI X has been assessed for GWI, and neither has been studied using assessment of pro inflammatory biomarkers.

The primary aim of this study is to determine whether nasal irrigation using a participant controlled protocol improves upper respiratory and fatigue symptoms among participants with GWI. We hypothesize that routine care plus either form of NI will be more effective than routine care alone.

Our secondary aims are:

- To explore whether use of NI is associated with changes in the inflammatory marker concentration nasal in mucus and serum.
- To explore whether use of NI is cost effective and satisfying to participants.
- To explore the ability of pretreatment psychosocial and clinical characteristics to predict which patients will benefit most from the two forms of NI.

2. Materials and methods

2.1. Study design

The study is a 26 week, three arm randomized controlled trial (RCT) to assess the comparative effectiveness of three therapeutic approaches in patients with GWI affected by CRS and fatigue. All groups will utilize routine care for their symptoms of CRS and fatigue. Group 1 will add NI with saline (NI S) twice daily and Group 2 will add NI with xylitol (NI X) twice daily to their usual care regimen. Group 3 will continue to use routine care only.

2.2. Eligibility

Eligibility is based on self report. Potential participants will be initially screened by phone and then in person at a later date. Inclusion criteria include (1) deployment to the Persian Gulf for the purpose of Operation Desert Shield or Operation Desert Storm during the first Gulf War (1990–1991); and (2) a diagnosis of GWI as based on a modified application of the “Kansas” GWI case definition [4]. The modification to this case definition involves making some of the exclusionary diagnoses relative, rather than absolute, if persons are stable with respect to the condition, and symptoms are well controlled/in remission, and have not resulted in hospitalizations within five years prior to enrollment. These diagnoses include diabetes, heart disease, stroke, melanoma, alcohol or drug dependence, depression, cancer, liver disease, posttraumatic stress and bipolar disorders: (personal communication with content expert Lea Steele, 8/26/12) [4]; (3) Eligible participants must also have a diagnosis of CRS which is defined by the presence for more than 12 weeks of 2 or more major factors (facial pain, nasal obstruction/purulence, hypo/anosmia, purulence in the nasal cavity) or one major and two minor factors (fever, headache, cough, fatigue, ear pain, dental pain, ear pain/fullness); and (4) self reported average daily sinus and fatigue ratings of moderate to severe grades over the past month [22] as indicated by at least 3 points on a 0–10 ordinal response symptom severity scale [22] (Table 1).

Exclusion criteria include self reported pregnancy; current use of NI, neurological or musculoskeletal conditions that could facilitate aspiration, or patients who otherwise cannot physically perform the NI procedure; anatomical abnormalities detected on CT or nasal endoscopy concerning for neoplasm perforations; and unstable psychiatric illness and competency as determined by psychiatric evaluation prior to enrollment. “Kansas definition” exclusions of lupus, multiple sclerosis, schizophrenia, active cancer treatment and presence of cognitive or physical impairments following a stroke remain absolute exclusionary criteria.

2.3. Recruitment and consent

Veterans will be recruited from the Madison and surrounding area. Recruitment from VA hospitals is based on an active duty screen which identifies veterans who were in the first Gulf War, and on an ICD 9 billing record screen to identify those diagnosed with CRS (473.*) and fatigue (780.7), or multiple episodes of acute rhinosinusitis (461.9) in the past two years. Potentially eligible participants receive a letter with an ‘opt in/

Table 1
Inclusion/exclusion criteria.

Inclusion criteria
<ul style="list-style-type: none"> • 35–65 years • Deployment to the Persian Gulf for the purpose of Operation Desert Shield/Storm during the first Gulf War (1990–1991) • Diagnosis of GWI as based on the “Kansas” GWI case definition [4] • Diagnosis of CRS • Moderate-to-severe sinus symptom impact (≥ 3 points on a 0–10 ordinal response scale) [22] as assessed by the single item: “What has been the average level of your sinus symptoms daily over the past month on a 0–10 scale” • Moderate-to-severe fatigue severity (≥ 3 points on a 0–10 ordinal response scale) as assessed by the single item: “What has been the average level of your daily fatigue over the past month on a 0–10 scale”
Exclusion criteria
<ul style="list-style-type: none"> • Self-reported pregnancy • Current use of NI or nasal spray • Self-reported neurological or musculoskeletal conditions that could facilitate aspiration, or patients who otherwise cannot physically perform the NI procedure • Self-reported borderline personality disorder • Severe or unstable mental health problems • Concern for neoplasm on computed tomography scan and/or endoscopy

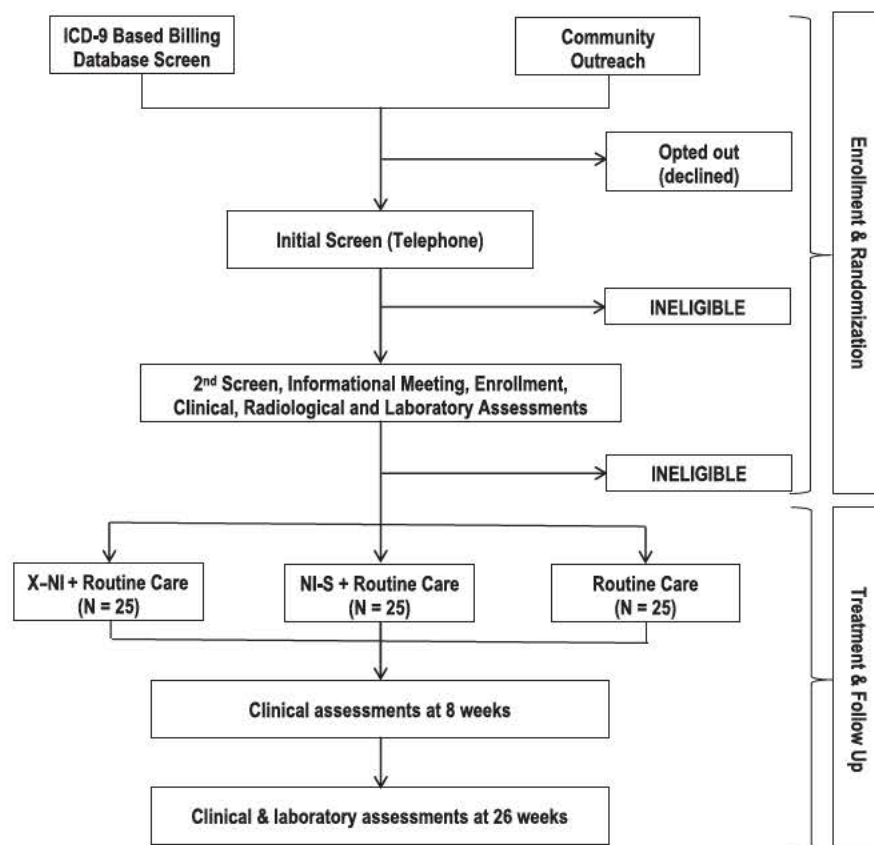
GWI, Gulf War Illness; CRS, chronic rhinosinusitis; NI, Nasal Irrigation.

opt out’ card inviting them to participate in an initial phone screen or declining further contact. Community outreach efforts will include local advertisements and collaboration with local veterans’ service organizations to access Gulf War veterans who may not use VA health services.

Informed consent process will be obtained in a two stage process. Verbal informed consent will be obtained prior to the initial telephone screening, and written informed consent will be administered in person at the in person screening visit (Fig. 1).

2.4. Participant assessment procedures

After phone based screening, interested eligible persons will be invited to a private, in person meeting at the UW Clinical Research Unit (CRU) lasting approximately 3 h. The CRU is a state of the art clinical research facility located within the University of Wisconsin Hospital and Clinics, and is funded by an NIH Clinical And Translational Science Award (CTSA). The session is divided into 2 parts. The first part will take approximately 20 min during which the research coordinator describes the study goals, procedures, activities and possible alternatives, and answers all questions. Education about the



ICD 9, International Classification of Diseases 9 Code; NI X, Nasal Irrigation Xylitol; NI S, Nasal Irrigation Saline

Fig. 1. Recruitment/randomization flowchart. ICD-9, International Classification of Diseases-9 Code; NI-X, Nasal Irrigation-Xylitol; and NI-S, Nasal Irrigation-Saline.

study will be assisted by the use of a Power Point slide presentation and a 30 second film about NI. Following this, interested prospective candidates will provide written consent for part 2 of the screening and study participation, and sign Health Insurance Portability and Accountability Act (HIPAA) forms, prior to further screenings. Interested eligible persons will then be enrolled, receive a study identification number and undergo baseline data collection. They will then be randomized to NI S, NI X or routine care alone using a computer generated block design with blocks of three. Participants will learn of group assignment after completion of eligibility determination, completion of baseline questionnaires and enrollment; they will open an opaque envelope containing a card containing group designation.

2.5. Measurement

To meaningfully understand GWI and the potential effectiveness of nasal irrigation on CRS and fatigue, we will assess baseline and ongoing participant status using a multidimensional suite of assessments including sinus computed tomography (CT) scan (baseline only), validated questionnaire instruments for overall quality of life, sinus and fatigue symptoms, and serum and nasal biomarkers. Data will be collected on costs related to sinus and fatigue during the study period, including self reported physician visits, related tests and medications (Table 2). Allocation will be concealed from assessors at baseline and follow up time points and blinding will be assessed using a short questionnaire.

2.6. Baseline participant characteristics

A sinus CT scan, the gold standard imaging modality to evaluate CRS severity [19], will be used to assess the baseline radiologic severity of CRS. CT findings indicative of CRS include mucosal thickening, bone changes, air fluid levels, obstruction of the sinus ostia, and polypoid. CT imaging correlates to the presence or absence of paranasal sinus disease in those patients with suggestive symptoms. The CT images will be evaluated by an ENT (TK) surgeon using the Lund McKay staging system, a validated and reproducible tool well suited for use in clinical research [20]. We will also assess baseline status using nasal endoscopy (TK). Endoscopic findings will be scored based on a modified grading system based on that described by Lund and Mackay [20]. Polyps are graded as absent (0), present in the middle meatus (1), or present beyond the middle meatus (2). Discharge is graded as not present (0), thin (1), or thick and

purulent (2). Edema will be graded as absent (0), mild (1), or severe (2).

Mental health status is an important prognosticator of adherence to chronic therapy. The Mini International Neuropsychiatric Interview (MINI) will be used to characterize potential subjects whose mental health precludes their safe and/or reliable study participation. The MINI is a structured neuropsychiatric interview developed specifically to assess major Axis I disorders as based on the DSM IV criteria. The reliability and validity of the MINI have been confirmed in previous studies [21].

2.7. Interventions

Participants in the nasal irrigation groups will be instructed on the irrigation technique using a slide presentation, short film, and live demonstration. Saline and xylitol irrigant will be delivered to the nasal cavity using a nasal irrigation cup (“neti pot”), a simple hand held vessel that uses the force of gravity to gently irrigate the user’s nasal cavity (<http://sinucleanse.org/company/about.htm>). Participants are instructed to irrigate the nasal cavity twice daily. The irrigation procedure has been used in prior studies [24].

Participants will mix the irrigant using salt or xylitol powder provided in individual use sachets using room temperature distilled water. The neti pot spout is inserted into one nostril and the head tipped; irrigant solution enters the nasal cavity, proceeds toward the back of the nose, traverses the posterior margin of the nasal septum, washes over the nasal mucosa and structures within the nasal cavity, then proceeds anteriorly and exits the nasal cavity via the contralateral nostril. The procedure is then repeated on the other side. The irrigant volume is 120 mL per nostril per irrigation session.

2.8. Nasal irrigation solutions

NI S solution is made with using a pre packaged commercial product containing salt and sodium bicarbonate that produces a 2% saline solution using a protocol tested in prior clinical trials (<http://sinucleanse.org/company/about.htm>) [11]. NI X solution is made with crystallized xylitol pre packaged for use in this study by the manufacturer (http://www.danisco.com/food_beverages/). The NI X is a 5% xylitol solution, and has been used in prior NI safety and clinical trials [15,17]. The individual xylitol sachets contain 6.25 g of xylitol powder for dissolution in 120 ml of distilled water.

Table 2
Study measurements.

Measures	Baseline	8-week	26-week
• The Sinonasal Outcomes Test (SNOT-20) [23]	*	*	*
• Multidimensional Fatigue Inventory (MFI) [25]	*	*	*
• The Medical Outcomes Survey Short Form-36 (SF-36) [26]	*	*	*
• Baseline Mini International Neuropsychiatric Interview (MINI) [21]	*		
• Economic cost-effectiveness	*	*	*
• Subject treatment satisfaction	*	*	*
• Nasal irrigation calendar and medication use log	*	*	*
• Baseline nasal endoscopy	*		
• Baseline sinus computerized tomography (CT) scan	*		
• Blood draw and nasal swab/wash to for pro-inflammatory cellular and cytokine profiles	*		*

2.9. Primary outcome

Sinus disease specific health related quality of life will be measured using the total score of a validated 20 item Sino Nasal Outcome Test (SNOT 20), a recommended tool for clinical trial research involving CRS [22,23]. The SNOT 20 is a reliable and valid outcome measure for patients with CRS (Cronbach's α 0.9, test retest $r = 0.9$); it describes the health burden and is sensitive to clinical change [23]. Patients who are more affected by CRS tend to have greater SNOT 20 scores ($P < 0.01$). The SNOT 20 score is expected to improve in NI treated subjects compared to controls; findings in a prior RCT assessing NI S in the general population are consistent with the above evidence [18,24].

2.10. Secondary outcomes

Fatigue will be assessed using the Multidimensional Fatigue Inventory (MFI) [25], a validated disease specific outcome measure for fatigue. The instrument has good internal consistency (average Cronbach's alpha 0.84) as well as established construct and convergent validity [25].

Overall health related quality of life will be assessed using the Medical Outcomes Survey Short Form 36 (SF 36), a validated questionnaire designed to assess health status, function and overall health related quality of life [26]. The SF 36 has good internal consistency and discriminant validity. The SF 36 has broad clinical application and has been validated in a variety of clinical and non clinical samples. GWI and CRS both affect sleep and breathing parameters. Prior studies suggest that both may be improved with NI S in some subjects. We have therefore augmented the SF 36 with eighteen relevant sleep and breathing related questions from the Wisconsin Sleep Cohort [27] questionnaire and the Asthma Control Test [28] respectively.

Economic cost effectiveness will be derived from self report of personal and medical care costs of subjects. The costs of the interventions will be calculated based on comparable charges for patients not enrolled in a research study. Effectiveness of each study intervention will be defined as the proportion of subjects who have at least 50% improvement in sinus related quality of life as assessed by the SNOT 20 questionnaire at the 26 week follow up. The cost effectiveness ratio (CER), reported as the “dollars spent per subject restored to health,” will then be derived by dividing the average cost of the intervention by the average effectiveness. The CER will be compared between the NI groups and a control group [29–31].

Subject treatment satisfaction will be assessed using two single item questions (7 point Likert scale) evaluating subject treatment satisfaction and a perceived global change [32,33]. In addition, at 26 weeks subjects will also be asked about their treatment experience using a semi structured 30 minute qualitative exit interview that will be recorded for transcription and evaluation of the study [34]. Very little qualitative work has been done in the field of GWI and NI. Qualitative studies have been used to good effect in the understanding of illnesses such as chronic fatigue syndrome [35].

2.11. Tertiary outcomes

CRS and fatigue symptoms overlap in many patients, with fatigue being a “minor” criterion in the formal diagnosis of CRS

[22]. Management of CRS symptoms by medical or surgical means [24,36] has been reported to alleviate fatigue. They may therefore be associated at an underlying biological level. The inflammatory response may be both a specific response to infection and injury, and a reflection of the body's integrated reaction to many other challenges to homeostasis, including stress and fatigue [37]. The inflammatory bias may also respond to therapy compared to control. Laboratory assessments of stress and illness sensitive biomarkers will therefore include serum based complete blood count, sedimentation rate, C reactive protein, Interleukin (IL) 6 levels and its soluble receptor. In addition, nasal inflammatory markers such as eosinophils, neutrophils, and cytokines IL 6, IL 10 and IL 12 will also be evaluated and quantified [38]. These will be obtained via an antecubital blood draw and nasal wash conducted at baseline and 26 weeks.

Bias will be minimized by a clinical protocol designed to offer maximum possible masking in a study of a physical procedure such as nasal irrigation. Participants in the two irrigation groups will be able to taste salt vs sugar based irritant. They will be told that it is not known whether NI with either solution compared to routine care is effective for treating sinus and fatigue symptoms in GWI. Furthermore, outcomes data will be collected by telephone or in person interviewers masked to treatment assignment. Because the saline and xylitol irrigants can be tasted, we will make every effort to assess core outcomes including the SNOT 20, MFI and SF 36 prior to side effects, limiting bias. We will also assess blinding of the assessor at 8 and 26 weeks.

3. Data collection and management

We will collect outcomes information at all stages of recruitment, randomization, and treatment processes; the trial will be reportable according to CONSORT guidelines. We will record the number of potentially recruitable patients, invitation letters sent, responses received and their resolution and the number of assessment sessions attended. Follow up data will include the number at each follow up, the number of participants completing the trial, and the number of withdrawals due to all causes.

Handling procedures for data transfer, entry and subsequent maintenance will be performed by a data manager (LZ). For our study we have developed a Research Electronic Data Capture (REDCap) [39] database to track data on each stage of recruitment, randomization, treatment, and treatment outcomes and will be able to report each in an integrated fashion. REDCap database provides data management, functionality, and support for study data capture. REDCap offers: 1) an interface with data validation for data captured on forms and surveys; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to SAS statistical package; 4) reporting capabilities; 5) procedures for importing data from external sources and 6) capabilities to grant user access rights to study data.

REDCap uses MySQL databases via a secure web interface with data checks during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user based privileges, and integration with the institutional LDAP server. The MySQL databases and the web server are both housed on secure

servers operated by the UW Department of Family Medicine (DFM). The servers are in a physically secure location and are backed up nightly, with the backups stored in accordance with the DFM ITS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The DFM servers provide a stable, secure, well maintained, and high capacity data storage environment, and both REDCap and MySQL are widely used, powerful, reliable, well supported systems. Access to study data in REDCap is restricted to IRB approved members of the study research team by username and password.

We will use electronic methods to routinely transfer data from the UW secured servers including the Online Collaborative Research Environment (Oncore); and REDCap [39] data bases prior to study analyses. Data handling processes were tested prior to the start of recruitment. The data manager wrote a detailed code book to facilitate analysis and data sharing. Requests for data will be reviewed by the senior author (DR) and our primary statistician. Representatives from the US AMRMC are eligible to review study records per research funding announcement guidelines.

4. Protection of human subjects

The study was approved by: 1) University of Wisconsin Madison Institutional Review Board, 2) United States Army Human Research Protection Office, 3) William S. Middleton Memorial Veterans Hospital Research and Development Committee and 4) Dupont Human Studies Committee (manufacturer of xylitol).

5. Data safety monitoring body

Standardized forms will be used for monitoring and reporting of side effects and adverse events. The principal investigator or a designated study physician will be present in case of a significant adverse event. The research staff will assess each subject monthly during the study with the following question: 'Do you think that you have had any side effects or problems with your sinus symptom therapy?' [If 'Yes'] 'Please tell me more about that.' Information regarding side effects and adverse events will be made available to the PI who will decide if the subject requires further medical care. The PI will report serious adverse events to the UW Research Subjects Advocate, the UW IRB and the project officer of the funding agency within 48 h. Reports will be made using the subject's ID number without other identifying information. Annual reports summarizing adverse events will be submitted to the Department of Defense under its guidelines.

In addition, in accordance with Department of Defense guidelines, we have assigned a medical monitor, a person otherwise unassociated with the study. The medical monitor will review all unanticipated problems involving risk to subjects or other serious adverse events, and all subject deaths regardless of their association with the protocol, and provide an unbiased written report of the event within 10 calendar days. He will comment on the outcomes of the adverse event and the relationship of the event to the protocol. The monitor will also indicate whether s/he concurs with the details of the report provided by the PI. Reports of significant events related or

possibly related to the protocol will be forwarded to the Department of Defense.

Unanticipated problems will also be reported to the IRB. In addition, any adverse events or problems will be reported to the VA in accordance with their reporting requirements. In the event of a suspected or actual data breach, the VA project officer and information security officer will be notified within 1 h of the event.

6. Stopping rules

The trial will be stopped only if the UW patient advocate and the medical monitor determine continuation poses an unacceptable risk due to serious adverse events in one or more of the treatment arms. They could decide to terminate one of the arms of the trial or the entire trial. We have not proposed an interim analysis for efficacy and therefore have established no formal stopping rules. The trial is of modest sample size and even if one or both of the irrigation treatments reduce sinus symptoms more than usual care, we do not consider this an important enough reason to end the trial early. Previous trials of nasal irrigation have been of modest quality; we believe that this study is of sufficient duration and methodological rigor to more clearly evaluate the effectiveness of nasal irrigation for GWI.

7. Statistical issues

7.1. Sample size calculation

The sample size for this study was calculated based upon detection of a significant overall F test in a 3 arm trial, with a power of 80% and a type I error of 5% ($\alpha = 0.05$). Based on prior research [24], we assume that the two active treatment arms will report a 35% reduction in SNOT 20 symptom scores compared to baseline. The control group is expected to report no significant changes in the SNOT 20 scores from baseline. Assuming a 35% improvement in the active treatment arms, an effective sample size of 20 subjects per study arm would provide 80% power (1 Beta = 0.81) to detect a significant overall F test of difference in treatment effects between the groups. Assuming 20% loss to follow up or missing data, 25 subjects per study arm (3 N = 75) will be enrolled.

7.2. Data analysis

Descriptive analysis will be conducted on all data before formal testing of hypotheses. Baseline self reported subject characteristics of the 3 groups will be assessed to determine the randomization success. If significant baseline differences are found between the groups, they will be assessed as covariates. All questionnaires, including the primary outcome measure, will yield continuous variables. Repeated measures analysis of variance [40–42] will be used to test the hypotheses within each group at baseline and follow up points. Differences between the study groups will be analyzed at each time point in the repeated measures model, and comprehensively for the entire timeframe of the study. Statistical significance will first be assessed using the global F test; specific pair wise contrasts between groups will be performed if the overall F test is significant. Distributional assumptions will be tested, and

variable transformations will be applied if necessary. Missing data will be analyzed for the degree and possible reasons for missingness. Where appropriate, imputation methods will be applied.

Cost effectiveness will be analyzed using an econometric approach. We will compute the cost effectiveness ratios (CER) of the 3 study interventions. Subject's personal and medical care costs will be assessed through questionnaire and administrative data. The CER will be evaluated for each treatment arm to determine the most cost effective treatment. Because the distributions of ratios do not conform to standard statistical testing, bootstrap analysis will be applied to determine standard errors and statistical tests of significance in pairwise comparisons of the CERs [31]. The bootstrap analysis will be conducted by sampling equal sample sizes ($N = 25$) with replacement from the three study groups, calculating cost effectiveness ratios from the bootstrap iteration samples, and constructing CERs comparing pairs of treatment arms. Bootstrap samples will be repeated 1000 times. The median bootstrap sample will be used as the CER outcome, with confidence intervals from the 2.5th percentile to the 97.5th percentile iteration.

A qualitative interview will be analyzed using the qualitative study method of transcribed in depth long interview [34]. The interview which will be audio taped, then stripped of all identifiers except a code number and transcribed. Transcripts will be reviewed and discussed by the study team and major themes will be identified using a consensus approach consistent with prior SNI studies [43].

The statistical analysis of cytokine, eosinophil counts and neutrophil counts is complex; [6,7] there is no consensus about how to analyze multiple cytokines and cellular biomarkers. However, our analysis will be hypothesis driven. Consistent with our hypotheses, we are most interested in whether subjects show a pro inflammatory bias at baseline and whether that bias decreases in response to therapy. Therefore we will construct our analyses to address specific cytokines that in isolation or in combination have been identified as pro inflammatory. Examples include eosinophil count alone, and the combinations of IL 8 and neutrophils, and IL 1 β , IL 6 and TNF alpha. These concentrations or cell counts are continuous variables and will be statistically handled in the manner as described above for questionnaire based outcomes.

Compliance to twice daily NI therapy, and use of medical resources, will be assessed using daily calendar logs and submitted monthly. We will assess other variables as covariates, primarily focusing on gender, age and smoking status. Other variables include use of antibiotics, antihistamines, nasal steroids and decongestants, results of the baseline psychiatric, endoscopic and CT scores. For those covariates that are measured before treatment, tests of the assumption of independence of treatment and covariate will be conducted [44]. Propensity scores will be estimated and used as a single confounding covariate structure [45,46].

8. Results

This study is currently enrolling participants. Baseline demographic and clinical data on the first 10 participants suggest that balanced allocation through effective randomization of middle age adults (52.6 ± 7.03 years, 5 female); NI S, NI X and control groups contain 3, 3, and 4 participants respectively.

SNOT 20 and MFI scores of 45.9 ± 6.3 and 11.5 ± 2.3 suggest moderate symptom severity and that essential eligibility criterion are being met. Effective recruitment, enrollment, and follow up rates among initial participants suggest high project feasibility and robust data collection. Anecdotal evidence suggests that participants are satisfied with study procedures and adherence to NI in both intervention groups is high. Follow up data are pending.

9. Discussion

Effective therapy for the many symptoms of GWI continue to plague the estimated 100,000 affected returned veterans of the first Gulf War. Several studies have evaluated the effect of liquid NI S and NI X on chronic sinus symptoms in the general population and in the context of workplace related airborne irritants and allergies [47,48,13,14,18]. In one NI S study, fatigue among NI S compared to routine care improved but not by a significant margin [24].

The current study is designed to determine whether participants can effectively manage or mitigate respiratory and fatigue based symptoms using daily NI S or NI X with a patient oriented irrigation protocol. Statistically and clinically positive outcomes on the SNOT 20 proposed study would suggest that NI is an effective adjunctive treatment for CRS and fatigue in patients with GWI. This would provide immediate, practical benefits to individual patients and society at large through improved quality of life and decreased work related expenses associated with GWI, and medical resource use, including topical agents and antibiotics [24]. The study is also designed to investigate the mechanism of action of NI through the assessment of inflammatory serum and nasal mucosa biomarkers, the first study to do so. Inflammatory processes may contribute to the development and perpetuation of initially infectious illness and to resultant generalized fatigue. Evaluation of biomarkers may contribute to the understanding of GWI, and suggest research in more targeted therapy. Given the overlap between sinus symptoms and fatigue, positive findings in this study may also suggest that NI could be an effective, patient controlled safe and inexpensive therapy for returned military personnel and members of the general population.

A complete understanding of GWI and NI continues to elude the research community. This study will address aspects of both through a flexible NI use protocol that allows participants to optimize the therapy in a several intervention parameters. Positive results on the primary and secondary outcome measures carry the potential of high patient and societal impact for both GWI veterans and society in general.

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**Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness:
Preliminary data from a 3-arm randomized controlled trial.**

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Background: Gulf War Illness (GWI), a multi-system condition with substantive impact on quality-of-life, affects 1 in 7 Persian Gulf War (1990-91) veterans. The etiology is unclear; chronic sinus symptoms and fatigue are common. Nasal irrigation with saline (NI-S) or xylitol (NI-X) is reported to improve sinus symptoms and fatigue in the general population; neither has been assessed in GWI. NI-S is hypothesized to improve sinus symptoms by thinning, cleaning and clearing mucus and by improving the protective function of the nasal mucosa. NI-X is hypothesized to enhance mucosal cellular immunity. We therefore assessed effects of NI-S and NI-X on participants with GWI, sinus symptoms and fatigue.

Methods: This 3-arm federally-funded Phase 2 randomized controlled trial (Clinicaltrials.gov NCT01700725; target sample size; N=75) is enrolling participants with GWI, chronic sinus symptoms and fatigue. All groups use routine medical care; NI-S and NI-X participants add nasal irrigation twice-daily using 80 mL 2% saline or 120 mL 5% xylitol solutions made using distilled water. Primary outcomes include the validated Sinonasal Outcome Test (SNOT-20, 0-100 points) and the Multidimensional Fatigue Index (MFI). Secondary outcomes include pro-inflammatory cellular and cytokine profiles, cost-benefit analysis and participant satisfaction. Assessment is at baseline, 8 and 26 weeks. Intention-to-treat analysis of within- and between-group differences is by Mann-Whitney 'U' and Cohen's 'd' effect size tests.

Results: 36 participants are enrolled, 23 (74% male; 51.4±6.9 years old) have completed baseline and 8-week assessments. All groups improved SNOT-20 scores compared to baseline status; NI-S: 17.1±17.4 points, p=0.02; NI-X: 7.8±11.6 points, p=0.1; Control: 4.0±4.2 points, p=0.05). Within- and between-group differences on the MFI subscales were not statistically significant. Compared to SNOT-20 Control scores, NI-S scores showed moderate effect size (Cohen's $d=0.45$; $p<.001$); NI-X scores showed small effect size (Cohen's $d=0.17$, $p=0.07$). There has been one case of self-limited epistaxis.

Discussion: Preliminary data suggest that NI-S and NI-X may improve chronic sinus symptoms among participants with Gulf War Illness. Progress to date suggests robust study conduct, protocol adherence to nasal irrigation use, and satisfaction with care. Full enrollment, and eight-week data on secondary outcomes, and all 26-week data on current participants, are pending.